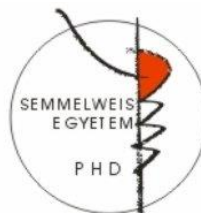


FLUID ASSESSMENT BY OBJECTIVE MEASURES IN END STAGE KIDNEY DISEASE

Ph.D. Thesis

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INTRODUCTION

Maintaining intravascular volume and blood pressure is essentially equivalent to maintaining life. Blood pressure is a critical vital sign that organisms try to preserve at all cost. The two central components of blood pressure is maintaining vascular tone and maintaining intravascular volume. While regulation of the fluid status has been studied and explored in the last century the assessment part of this seems to have been a more difficult element of fluid status maintenance.

There are physiological mechanisms in the kidney, carotid body and the heart among other sites of the body where this process is done. We will focus on how clinicians can assess the fluid status in the most vulnerable patient population, those with renal dysfunction. We will therefore investigate how best to assess fluid status in the End Stage Renal Disease (ESRD) population and we will offer two options for this.

The clinical task of accurately ascertaining patients' volume status seems quite easy. Physical exam is the part of the medical evaluation that may be most problematic, however. Many studies found it difficult to accurately ascertain fluid status by physical exam more accurately than 49%, some found the accuracy that pulmonary crackles had a sensitivity of 56%, S₃ third heart sound 20%, jugular venous distention 39% and edema 67%. Others found that sensitivities of peripheral edema detecting fluid overload ranged from 1-10% while lung crackles indicated instrument-detected pulmonary fluid overload 9-27% depending whether the pulmonary edema was deemed mild, moderate or severe. It is thus clear that physical exam in the dialysis patient population was similarly unable to give appropriate assessment for fluid status.

An alternative to physical exam-assessed fluid status is the use of a biomarker B-type Natriuretic Peptide (BNP) or a device such as the bioimpedance apparatus, BCM. Because cardiac hormones are degraded through the neutral endopeptidase (NEP) and NEP is expressed particularly abundantly expressed in the kidney its blood levels are higher in renal failure. Another method to assess fluid excess or perhaps deficit is through a device whose physics of BCM is based on the conductivity of various body compartments at different rates and resistance values. BCM "enables clear separation

between extracellular and intracellular water by the extremely wide range of measurement frequencies”.

OBJECTIVES

The dissertation will examine and present studies to the following question: What is the clinical importance of measuring fluid excess in the dialysis population?

The hypothesis of the dissertation is thus to show that using actual fluid space measurements by BNP or BCM improves care of the dialysis patient. Further, fluid management based on measured fluid spaces will decrease fluid overload, blood pressure and polypharmacy.

METHODS

Most of the studies discussed here are observational and cross sectional studies that entail two populations. Those patients whose fluid status had been measured by BNP are those who live in the North West Louisiana area of attrition, mostly elderly African Americans in the Veterans’ Affairs Medical Center.

In a prospective observational study of a sub-cohort of 19 consecutively admitted veteran patients (of a cohort of 97 dialysis patients) acutely hospitalized, needed acute dialysis. Their indications for hospital admission varied and their symptoms were often unrelated to volume overload. After conventional hemodialysis was started in the hospital, ultrafiltration (UF) was commenced based on the admission BNP value. The UF was targeted to achieve a BNP goal of 500 pg/mL. ... Since the target BNP was 500 pg/mL, patients were deemed volume-overloaded if the BNP was >500 pg/mL.”

The patient population of studies we performed using the bioimpedance was decidedly different from that of the BNP studies previously described. This was an East European population of all White people in Budapest, Hungary at Semmelweis University in a single chronic dialysis facility operated by a for-profit chain provider (Fresenius Medical Care) as a contractor for the universal health care system paid by a single, state payer. Patients were treated at this facility from a single territory of no more than 50 miles radius and were all provided free transportation to and from the dialysis facility.

RESULTS

The ultrafiltration treatment protocol that continued fluid removal targeting a BNP value of 500 pg/mL made a very significant change in every measure we set out to improve. As a result of BNP-directed ultrafiltration body weight came down by 10.8 kg on the average and blood pressure decreased very significantly. Importantly, polypharmacy also decreased by an average of 1.5 antihypertensive medication as well as blood pressure also decreased: the systolic (by 21.5 mmHg) and diastolic readings (by 11.7 mmHg) and mean arterial pressure by 12.5 mmHg.

The patient population in Hungary for the bioimpedance studies had a mean vintage of 66.5 ± 57.1 months (range, 2–312 months) and a residual urine output of 442 ± 521 mL/day. “We found a significant correlation between OH and systolic blood pressure ($r = 0.39$; $p = 0.0006$) with each liter of OH generating 3.6 mm Hg. There was a positive correlation between the number of antihypertensive medications and the degree of OH that held true even when those patients with no blood pressure medications and those with five or more medications were excluded ($r = 0.33$; $p = 0.047$).”

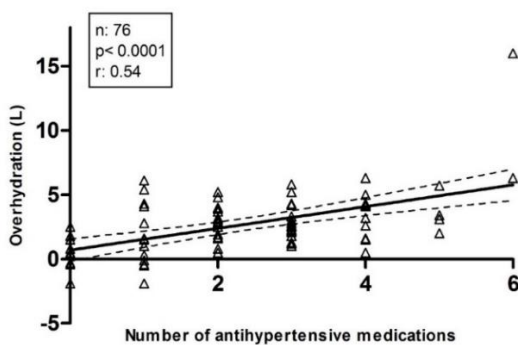


Figure 1. The number of antihypertensive medications and overhydration

The number of antihypertensive medications has a strong relation with the degree of overhydration. $n = 76$, $p < 0.0001$, $r = 0.54$

Additionally, the use of diuretics in dialysis patients does not seem to prevent fluid excess, in the presence of diuretics D (+), the degree of overhydration is significantly greater than in its absence D (-). $p = 0.003$.

In a study where we compared BNP values and BCM measurements we found that there was a strong correlation between the two types of measurements. “Our data analysis included an evaluation of correspondence between the two methods, BNP values or OH%. We found that the linear regression analysis describing this relationship could be expressed with the equation of $y = 209.83x - 1133.4$ ($r = 0.6996$)”. “The ROC revealed a significant correspondence, with the AUC 0.885 for the BNP when the OH% was set to 15% of OH or greater.”

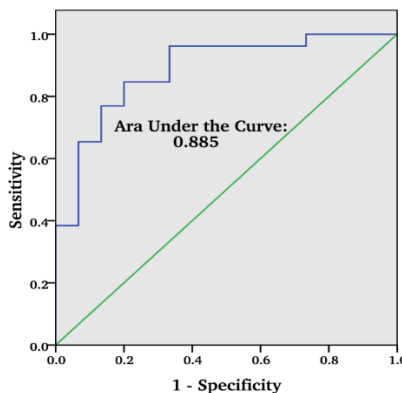


Figure 2. “Area under the curve (AUC) for the receiver operating characteristic (ROC) curve for the BNP when the discriminating threshold between overhydration and normohydration is used as 15% of the extracellular water.”

Fluid excess has been demonstrated to increase mortality in the dialysis population. In a landmark study Wizeman and co-workers showed that a volume overloaded state by

more than 15% of the extracellular volume increased mortality significantly. At the same time hypertension, just as in many other studies, was not directly related to mortality, HR: 0.986 (90% CI: 0.979-0.995 $p = 0.014$); hypertension in fact seems to provide a certain degree of protection... Additionally, a Turkish study found that a strict fluid or volume control will improve survival. Thus the mandate of driving the ultrafiltration by some objective measurement rather than physical exam alone is strong. Ozkahya also showed that blood pressure can significantly be improved all the while the number of antihypertensive medications are decreased provided the intravascular fluid status is improved by decreasing it according to some kind of objective guide.

As a response that clinicians need to guide their management of hypertension and fluid status based on objective measurements were the studies presented before. The underlying problem is that physical exam is just simply not objective enough and simply unable to assess a patient's fluid status enough to safely guide therapy. Physical exam when compared with an objective measurement do not measure up. "Lung congestion by crackles, edema, or a combination thereof poorly reflected the severity of congestion as detected by ultrasound B lines" or when compared to BNP measurements.

What the presented papers and clinical studies using BNP or BCM have shown is an alternative to "driving blindly". There is no reason why biomarkers such as BNP should not be used in the regular clinical practice. In our study where we directed our UF procedure according to the BNP values of acute hospitalized, chronic dialysis patients we demonstrated that this method was clinically usable and applicable but even more importantly, it improved care. Relying solely on physical exam in our BNP study of hospitalized patients would have missed 50% of the volume overload. Thus physical assessment is as good as a coin toss!

The third benefit of BNP directed ultrafiltration is the improvement of blood pressure control. The above article has demonstrated that removal of fluid will decrease blood pressure and discontinuation of antihypertensive medications become a possibility

Polypharmacy, is dangerous not only because of the financial burden it involves but firstly because of the drug-drug interactions and the side-effect profiles that patients accumulate when taking more and more medications. Pill burden is another concern as

that is a known risk for patient non-adherence. A DOPPS study has demonstrated that taking too many pills will decrease compliance with phosphate binders. Taking phosphate binders is critically important, dialysis patients who use phosphate binders have a survival advantage over those who do not. The clinical benefits of blood pressure control in dialysis patients with antihypertensive medications is a matter of controversy. The idea of decreasing blood pressure is in the hopes to decrease mortality, cardiac events or stroke. This, among dialysis patients, however, has not been demonstrated so clearly by the literature. It is well known that good dialysis, done over long hours and aiming to achieve dry weight can achieve both a good blood pressure control and good survival, with a very small amount of antihypertensive medications.

In a cross sectional study in a North-West Louisiana chronic dialysis cohort we counted how many antihypertensive medications our patients took without change in dose or new prescription for at least 2 months and compared that to their actual pre-dialysis blood pressures. We found that the more medications patients received the higher their blood pressure ended up being.

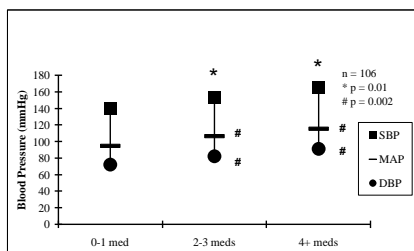


Figure 3. Mean blood pressures grouped according to the number of medications
 “Mean blood pressures (BPs) grouped according to the number of antihypertensive medications. SBP, systolic BP; MAP, mean arterial pressure; DBP, diastolic BP”

The relationship of hypertension, antihypertensive medications and outcome in dialysis patients may be explained by all the above investigations presented and therein lies the clinical utility of objective fluid assessment, by any method. We have shown that escalating antihypertensive medications, giving more and more medications to dialysis patients in fact does not improve their blood pressure control, or is not associated with

a better blood pressure control. We have, however, demonstrated fluid excess is associated with higher blood pressure and higher number of antihypertensive medications. Furthermore, fluid removal will decrease blood pressure and polypharmacy.

Successful fluid removal may eliminate the excess mortality risk described by Wizeman. Onofriescu has also shown that patients whose dry weight was managed with bioimpedance versus those whose dry weight was managed based on clinical judgement only – or any other objective measure of fluid status – had better survival.

CONCLUSION

What this dissertation has done is the integration of the previously proposed method of blood pressure control in dialysis patients and demonstrating in clinical practice how it can be done successfully. These studies have demonstrated that the safe way to go from polypharmacy and volume overload is to slowly decrease patients' weight while decreasing the antihypertensive medication burden. This can be done in a safe way by continuously monitoring their volume status by the use of BNP or BCM — “turn the lights on when driving at night”. These clinical studies have all lined up in a string of idea that blood pressure control ought to be done not by medications but by eliminating the cause of hypertension. We should treat hypertension with minimal antihypertensive drugs in the dialysis population so that we can eliminate the greater mortality risk factor: volume overload. We ought to use one of these instruments to control fluid status safely. For the first time we demonstrated that BNP or BCM-directed fluid control actually improves care!

The conclusions therefore include that fluid overload can be safely decreased when objective measurements guide therapy. Polypharmacy can be improved with BNP- or BCM- directed ultrafiltration and an excessive number of antihypertensive medications impede volume control.

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